REMARKS

The Examiner rejects claims 1-16 in the subject application. Applicants amend claims 1, 3 and 16. Applicants cancel claim 8. Claims 1-7 and 9-16 (2 independent claims; 15 total claims) remain pending in the application.

Support for the various amendments may be found in the originally filed specification, claims, and figures. No new matter has been introduced by these amendments. Reconsideration of this application is respectfully requested.

SPECIFICATION

The Examiner objects to the abstract of the disclosure because formula (I) of the fluorescent structural portion is missing. Applicants have amended the Abstract accordingly, thus, obviating the Examiner's objection. Applicants have also amended various paragraphs in the specification to correct a typographical error in chemical formulas (I) and (III).

35 U.S.C. §112 REJECTION

The Examiner alleges that it is unclear how "R," not being a terminal group, can react with a protein to form a covalent linkage. The Examiner contends that to form a covalent bond with a protein, the functional group "R" needs to be a terminal group. Applicants have appropriately amended the claims to reflect that "R" is a terminal group, thereby clarifying the Examiner's allegation.

Next, the Examiner contends that in claims 1 and 16 the valency of carbon is incorrect because the terminal carbon cannot accommodate a bonded carbon atom and four fluorine atoms. Applicants have correspondingly amended the claims to reflect that the carbon depicts a proper valence balance. This amendment obviates the Examiner's contention.

Finally, the Examiner rejects claim 1 under 35 U.S.C. §112 (second paragraph) asserting that claim 1 is incomplete for omitting essential steps, wherein the omitted

steps are washing steps after binding of a first antibody, after sample application and binding, after addition of second antibody, and before measurement of fluorescence. Applicants amend claim 1 to recite, "wherein the method comprises a step of washing after each of steps (a) to (c)," thus obviating the Examiner's rejection.

35 U.S.C. §103 REJECTIONS

The Examiner rejects claims 1-16 under 35 U.S.C. §103(a) as allegedly being unpatentable over each of: 1) Yuan et al., Anal. Chem. 1998, Vol. 70, No. 3, pp. 596-601 ("Yuan") or Matsumoto et al., U.S. Patent No. 5,859,297 ("Matsumoto") and in view of 2) Pennanen et al., Int. J. Immunopharmacol. 1995, Vol. 17, No. 6, pp. 475-480 ("Pennanen"). Applicants respectfully traverse the rejection.

To anticipate a claim, the cited reference must teach each of the elements of the rejected claim. Among other elements, claim 1, as amended, defines a time resolved fluoroimmunoassay for detecting a cytokine in a biological fluid sample comprising,

> (a) a first antibody including a portion bound to a solid phase and a region bindable to a cytokine; (b) the cytokine; (c) a second antibody including a region bindable to the cytokine and a portion to which biotin is bound;

Applicants submit Yuan and Matsumoto fail, either individually or in combination, to teach, advise, or suggest each and every element of amended claim 1, from which claims 2-7 and 9-15 variously depend.

Yuan and Matsumoto, directed to the problem of detecting cytokines, disclose the use of a lanthanide chelating agent found to be sensitive when used in assays to *detect the tumor marker alpha-fetoprotein* (emphasis added). The skilled artisan would expect such a protein to be at a high concentration in the serum of the tumor-bearing patient, as the expression of tumor markers is up-regulated in such patients, and thus easy to detect. Therefore, any disclosure relating to the detection of such proteins would not lead one skilled in the art to assume that such could also be applied to

chemokines, which have a low effective or free concentration in serum. As such, one skilled in the art would not be prompted to incorporate the solution to the problem of Yuan or Matsumoto, namely, the use of BHHCT, to the problem to be solved by the invention of the current application.

As further evidence of Applicants argument, and as can be clearly seen from the journal article herein submitted[1] ("Leonard"), it was not possible to detect a chemokine in a biological fluid sample prior to the disclosure of the claimed invention. Specifically, this article explains that while chemokines are generally produced at higher levels than non-chemokine cytokines, chemokines are undetectable in normal human serum. Leonard explains that auto-antibodies are generated against both non-chemokine cytokines and chemokines as a mechanism of regulating the biological functions of these molecules. Importantly, free auto-antibodies rather than immune-complexes of antibodies and cytokines are readily detectable in normal human sera. Conversely, free auto-antibodies against chemokines are undetectable, such antibodies only being detectable as immune complexes with chemokines

Next, Pennanen is not a relevant prior art reference to combine with either Yuan or Matsumoto, as Pennanen is directed to screening the effects on drug secretion by macrophages in vitro, and Pennanen does not teach or suggest,

> measuring fluorescence of the fluorescent structural portion which has been complexed with the lanthanoid metal ion,
>
> wherein the method comprises a step of washing after each of steps (a) to (c); and
>
> wherein the cytokine is a cytokine belonging to the chemokine family, and
>
> wherein the fluorescent structural portion is represented by General Formula (I):
>
> $R\text{-}Ar\text{-}C(=O)\text{-}CH_2\text{-}C(=O)\text{-}C_nF_{2n}\text{-}X$ (I)

[1] Edward J. Leonard, Plasma Chemokine and Chemokine-Autoantibody: Complexes in Health and Disease (1998).

Wherein, the above comprises part of a sensitive assay for measuring chemokine levels in a biological fluid sample, as recited in the amended claim 1. As such, one skilled in the art would not be motivated to combine Pennanen with either Yuan or Matsumoto. Furthermore, there is no teaching, advising, or suggestion by Pennanen to combine with the teachings of Yuan or Matsumoto to disclose each and every element of the present invention as required.

Finally, the methods and kits of the amended claims make possible the detection of a chemokine in biological fluid samples, and that such could not be achieved by conventional techniques available in the art as of the priority date. This effect is an unexpected and significant effect which is qualitatively different from the effects of conventional techniques.

Accordingly, Yuan, Matsumoto, and Pennanen either individually or in combination fail to teach, advise, or suggest one or more of the claimed elements, thus claims 1-7 and 9-16 are patentable over them. Applicants respectfully request withdrawal of this rejection.

CONCLUSION

Applicants respectfully submit that the present application is now in condition for allowance. Reconsideration of the application is thus requested. Applicants invite the Examiner to telephone the undersigned if he or she has any questions whatsoever regarding this Response or the present application in general.

Respectfully submitted,

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By: _____
Robert A. Iussa
Reg. No. 51,337

SNELL & WILMER L.L.P.
One Arizona Center
400 East Van Buren
Phoenix, Arizona 85004-2202
Phone: (602) 382-6226
Fax: (602) 382-6070
Email: riussa@swlaw.com